

2103 Kansas Immunization Conference –
“Let’s Get the Word Out about Pertussis!”

Pertussis Update 2013

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Disclosure

- Neither I nor any member of my immediate family has a financial relationship or interest with any proprietary entity producing health care goods or services related to the content of this CME activity.
- My content will include discussion/reference of commercial products or services.
- I do not intend to discuss an unapproved/
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Objectives

- Describe the clinical characteristics and testing strategies for pertussis
- Define the epidemiology of pertussis in the era of acellular pertussis vaccine
- Assess reasons for recent resurgence of disease in the US
- Understand the role of physician in making a timely diagnosis, instituting treatment and recommending chemoprophylaxis in households and the role of vaccine in outbreaks
- Understand the implications of the recent azithromycin alert in treatment and chemoprophylaxis of pertussis

Road Map: Highest priority vaccine initiatives

- Pertussis
 - Still outbreaks 60 years after vaccine introduction
- Diarrheal disease and vaccines
 - Old target (rotavirus) vs new target (Norovirus)
- Influenza
 - Old strategy vs new options
- HPV vaccine-coverage remains low
- Conjugate polysaccharide vaccines
 - PCV7 to PCV13 transition; MCV4 with new Hib MnCY



Question 1

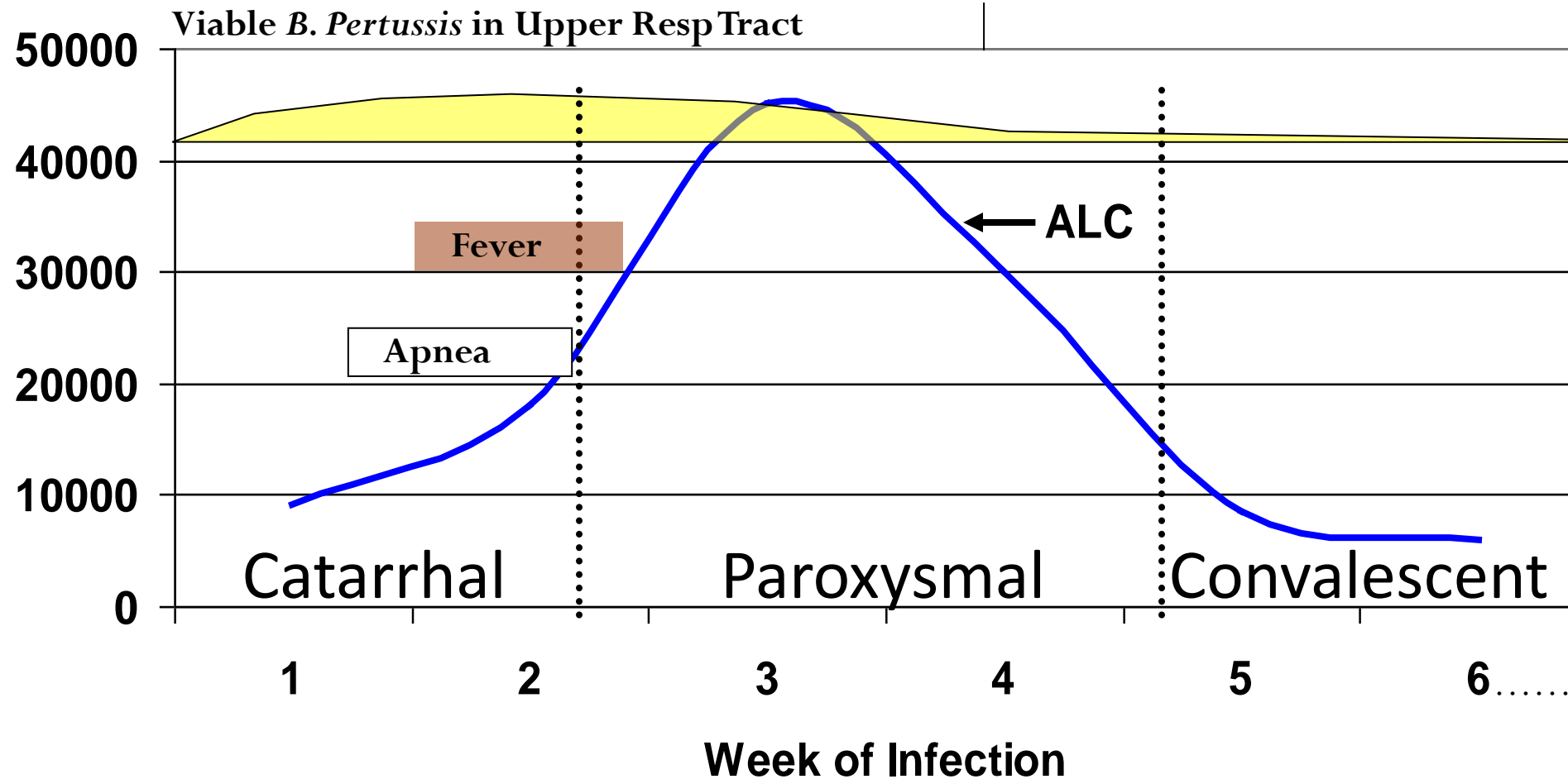
It is December 24th and a 3 month old former late preterm infant presents to the office at 4pm. He has not been immunized and has been coughing for 7 days. Which of the following is the most likely cause of his cough?

- A. RSV
- B. Adenovirus
- C. Pertussis
- D. Influenza virus
- E. Any of the above?

Pertussis basics

- Highly contagious bacterial RTI
- Incidence cyclical with peaks every 2-5 years
 - Peak 1934: >265,000 cases; nadir: 1976 1010 cases
- Morbidity in infants greatest
- Under-recognized in older population
- Resurgent disease in last decade

Pertussis Time Course



ALC = Absolute Lymphocyte Count

Question 2

Comparing the year 2011 (the era of aP vaccines), to 1922, what % decrease in pertussis cases has been noted in the US?

- A. 60%
- B. 75%
- C. 85%
- D. 92%
- E. 99%

20th Century and Current Annual Vaccine-Preventable Disease Morbidity

Disease	20th Century Annual Morbidity [†]	2011 Reported Cases ^{††}	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	212	> 99%
Mumps	162,344	370	> 99%
Pertussis	200,752	15,216	92%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	4	> 99%
Congenital Rubella Syndrome	152	0	100%
Tetanus	580	9	98%
<i>Haemophilus influenzae</i>	20,000	8*	> 99%

[†]Source: JAMA. 2007;298(18):2155-2163

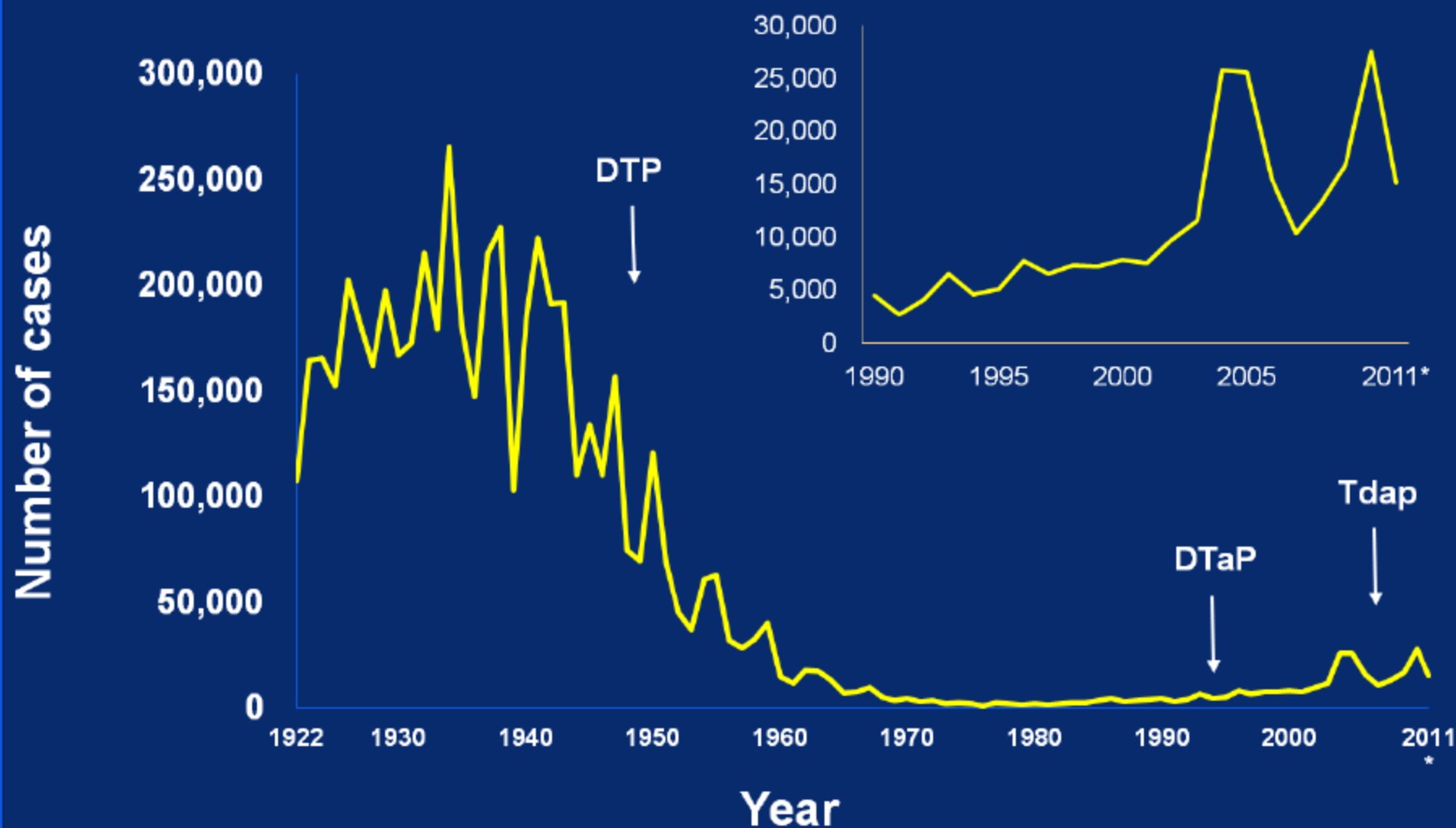
^{††} Source: CDC. MMWR January 6, 2012;60(51);1762-1775. (provisional 2011 data)

* *Haemophilus influenzae* type b (Hib) < 5 years of age. An additional 14 cases of Hib are estimated to have occurred among the 237 reports of Hi (< 5 years of age) with unknown serotype.

Pertussis Immunization in the US

- Whole-cell vaccines/DTwP (1940s)
- DTaP (1990s)
 - Infants at 2, 4, 6 months (1997)
 - Toddlers at 15-18 months (1992)
 - Pre-school at 4-6 years (1992)
- Tdap
 - Adolescents at 11-12 years (2005)
 - Adults who have not received (2005)

Reported NNDSS pertussis cases: 1922-2011

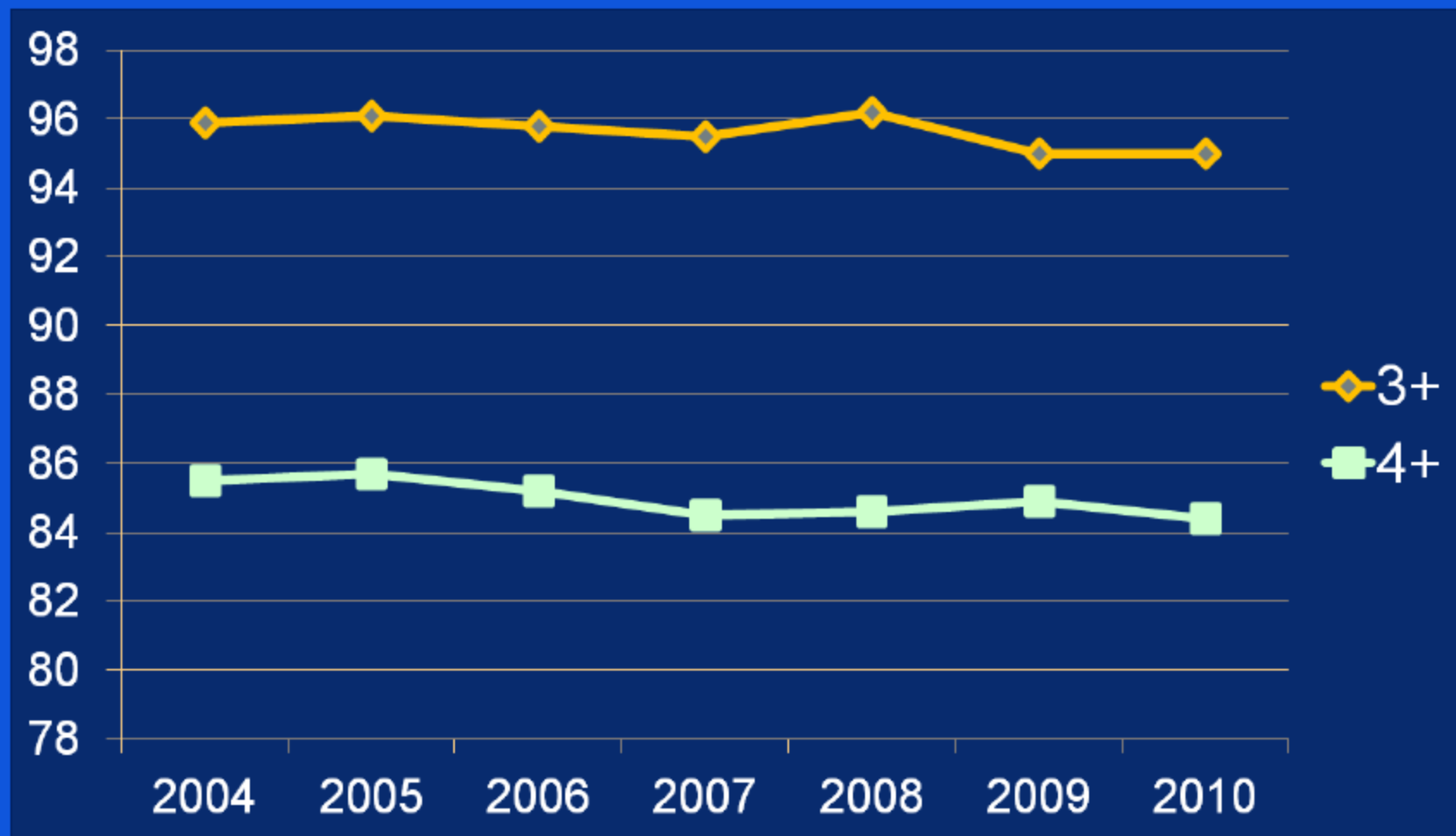


*2011 data are provisional.

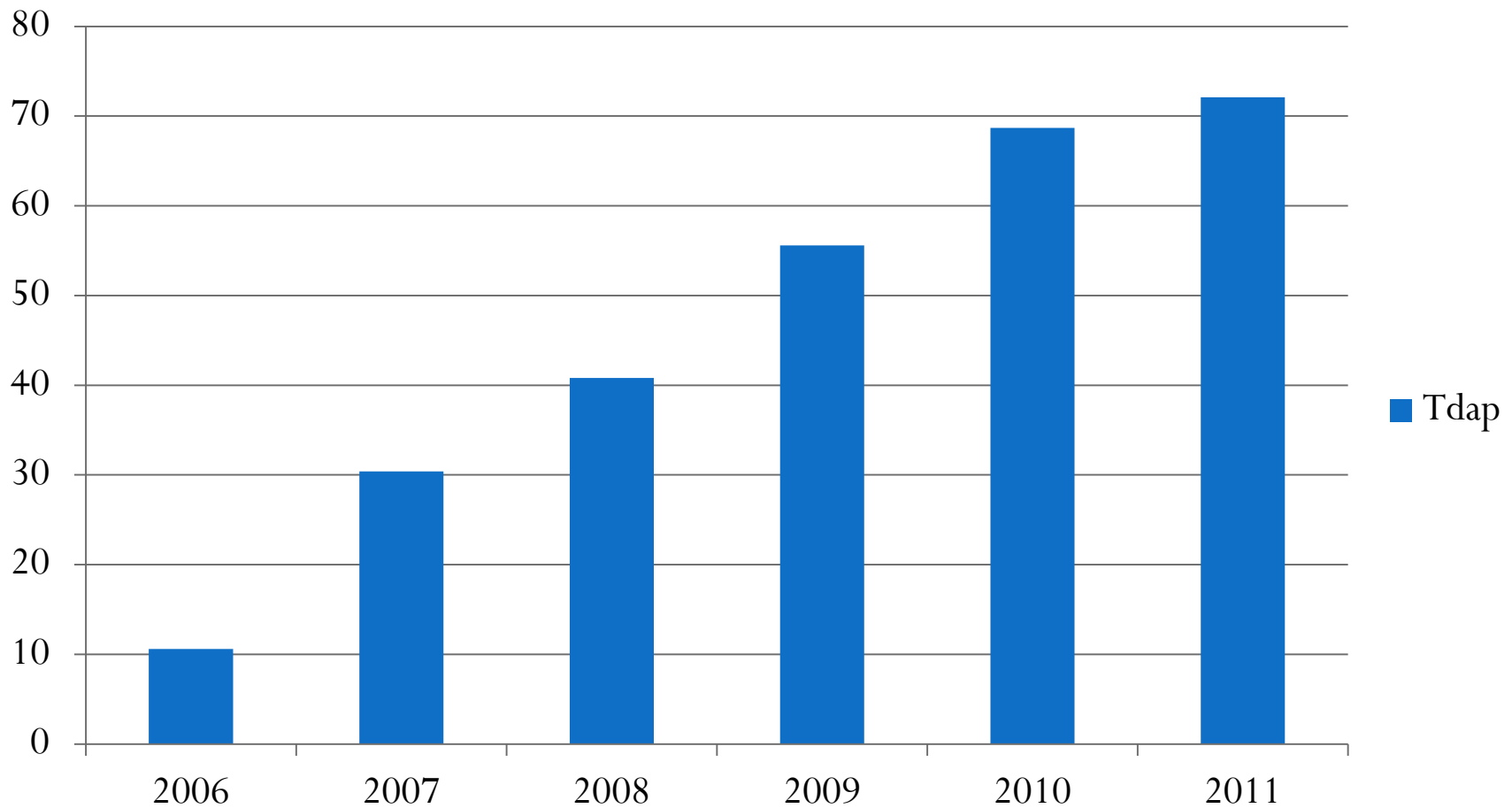
* 2010 NNDSS data are provisional

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949 passive reports to the Public Health Service

DTaP coverage among children aged 19 through 35 months — 2004–2010



Tdap coverage in adolescents (13-17 years), CDC surveillance data



States with $\geq 90\%$ in 2011: MA, NH, VT, IN

States with $< 70\%$ in 2011: SD, AR, **MS**, MN, GA, OK, SC, WV

Pertussis Cases Reported to CDC, by year

Year	Reported cases
2000	7867
2001	7580
2002	9771
2003	11647
2004	25827
2005	25616
2006	15632
2007	10454
2008	13278
2009	16858
2010	27550
2011	18719
2012	41880

Question 3

What is the most likely cause of the recent resurgence of pertussis in the US?

- A. Vaccine refusers have increased the pool of susceptibles
- B. Efficacy of acellular vaccines is inferior to whole cell vaccines
- C. Providers are more astute in making the diagnosis of pertussis
- D. Adolescents have not been immunized with Tdap
- E. The organism has mutated

Reported pertussis-related deaths by age-groups, U.S., 1980-2009

Age-Group	1980-1989 ¹	1990-1999 ¹	2000-2009 ²
0-1 month	38	68	152
2-3 month	11	16	24
4-5 month	5	5	2
6-11 month	7	4	1
1-4 years	13	2	2
5-10 years	1	6	3
11-18 years	0	0	3
>18 years	1	2	8
Total	77*	103	194

Includes one case with unknown age

¹ Vitek CR et al. *Pediatr Infect Dis J* 2003; 22(7):628-34.

² National Notifiable Diseases Surveillance System, CDC, 2009

California Pertussis Epidemic, 2010

Kathleen Winter, MPH¹, Kathleen Harriman, PhD, MPH, RN¹, Jennifer Zipprich, PhD¹, Robert Schechter, MD¹,
John Talarico, DO, MPH¹, James Watt, MD, MPH¹, and Gilberto Chavez, MD²

What lessons can we learn from one of the largest
state-wide pertussis outbreaks in the vaccine era?

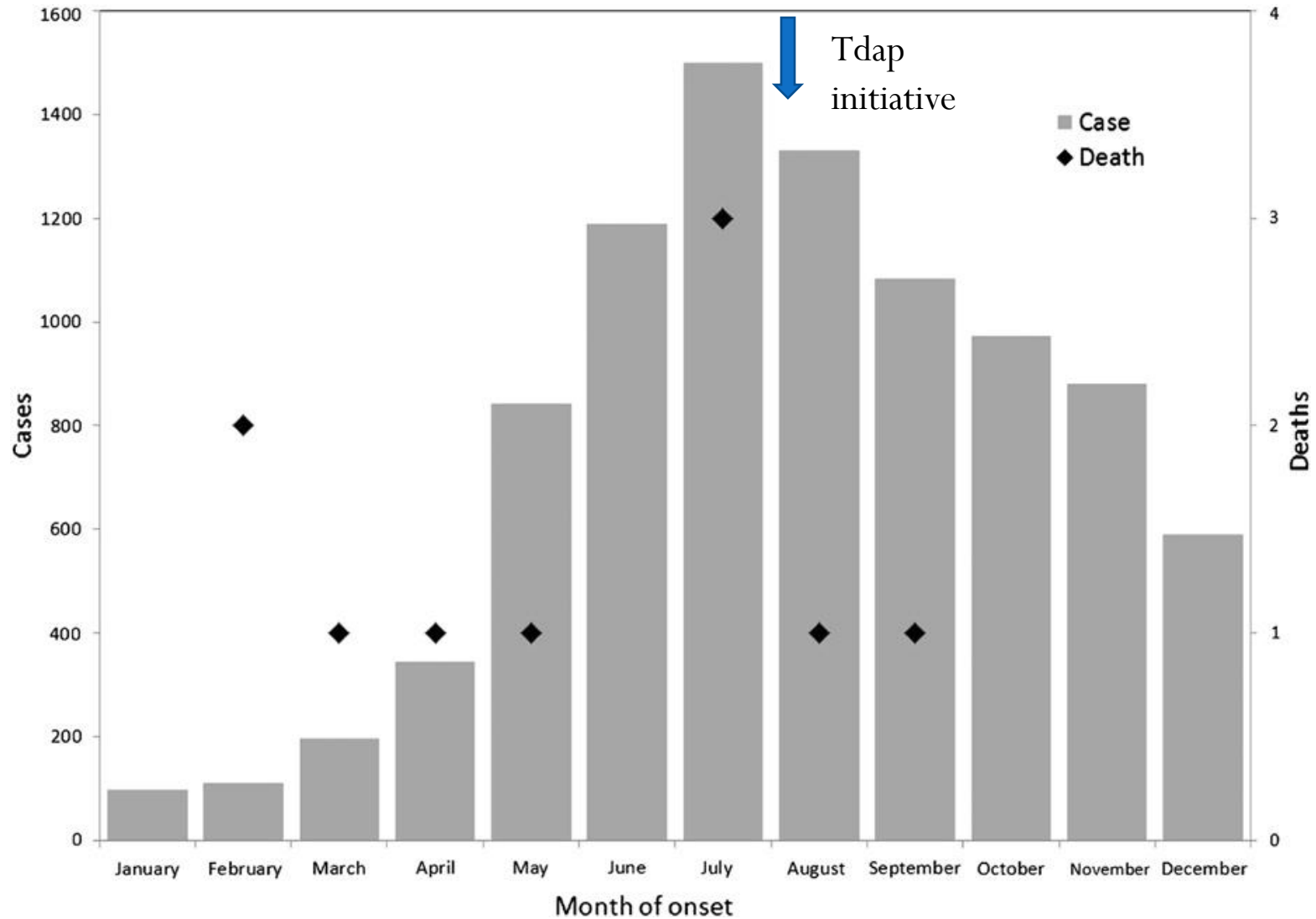
Methods

- Pertussis cases from 1 / 1 / 10-12 / 31 / 10 CDPH
- Specific criteria for diagnosis
- Surveillance data on clinical characteristics, patient demographics, vaccination status, clinical outcomes
- Incidence rates by using projected state population data
- Public health measures described

Results

- 9154 cases
 - Confirmed in 5482 (60%): cough plus +culture (6%) OR cough >2 weeks plus PCR (82%) or epi-link to confirmed case (12%)
 - Suspect in 1966 (21%): cough plus PCR (88%) or epi link AND at least one of the following-paroxysms, whoop or PTE
 - Probable in 19%: >2 weeks cough but no lab or epi-link

Epidemic curve of pertussis cases and deaths by month of onset: California, 2010



Hospitalization

- 809 (8.8%) hospitalized overall
- Among 720 infants < 3 months, 62% hospitalized with higher rates of hospitalization for Hispanic and Asian/Pacific Islander infants
- Median age at disease onset 2.6 months
- Median length of hospital stay 4 days (1-48 days)
- 285 pneumonia, 19 seizures, 3 encephalopathy

Pertussis deaths

- 10 deaths, all infants
 - 9 previously healthy
 - 1 preterm 2 month old
 - 9/10 Hispanic→52% of birth cohort in CA but 90% of deaths and 64% of cases in <6 month olds
 - Median WBC 78,000
 - 7/10 at least one visit and hospitalization; only 1 received macrolide antibiotic
 - Case fatality rate for infants < 3 months-1.3%

ALC and Pertussis

- A 3-week-old baby presents with cough and episodes of apnoea. Nasopharyngeal aspirate is negative for common respiratory viruses. You consider the diagnosis of pertussis and take a full blood count to assess the lymphocyte count.
- Leukocytosis with lymphocytosis (a white blood cell count of $\geq 20,000$ cells/mm³ with $\geq 50\%$ lymphocytes) in any young infant with an illness with cough is a strong indication of *B. pertussis* infection.
- A child with a normal lymphocyte count is unlikely to have pertussis. (Grade B)

Severe Pertussis

- Infants with more severe disease
 - Median peak WBC counts of 74,100 compared to 24,200 among infants with less severe disease
- All but one of those with more severe disease had at least a 50% increase in WBC within 48 hours
- Clinical features in those with severe infections: higher maximum heart and respiratory rates, pneumonia
- Conditions identified earlier after illness onset among infants with more severe disease.
 - Seizures, hypotension/shock, renal failure, intubation, exchange transfusion

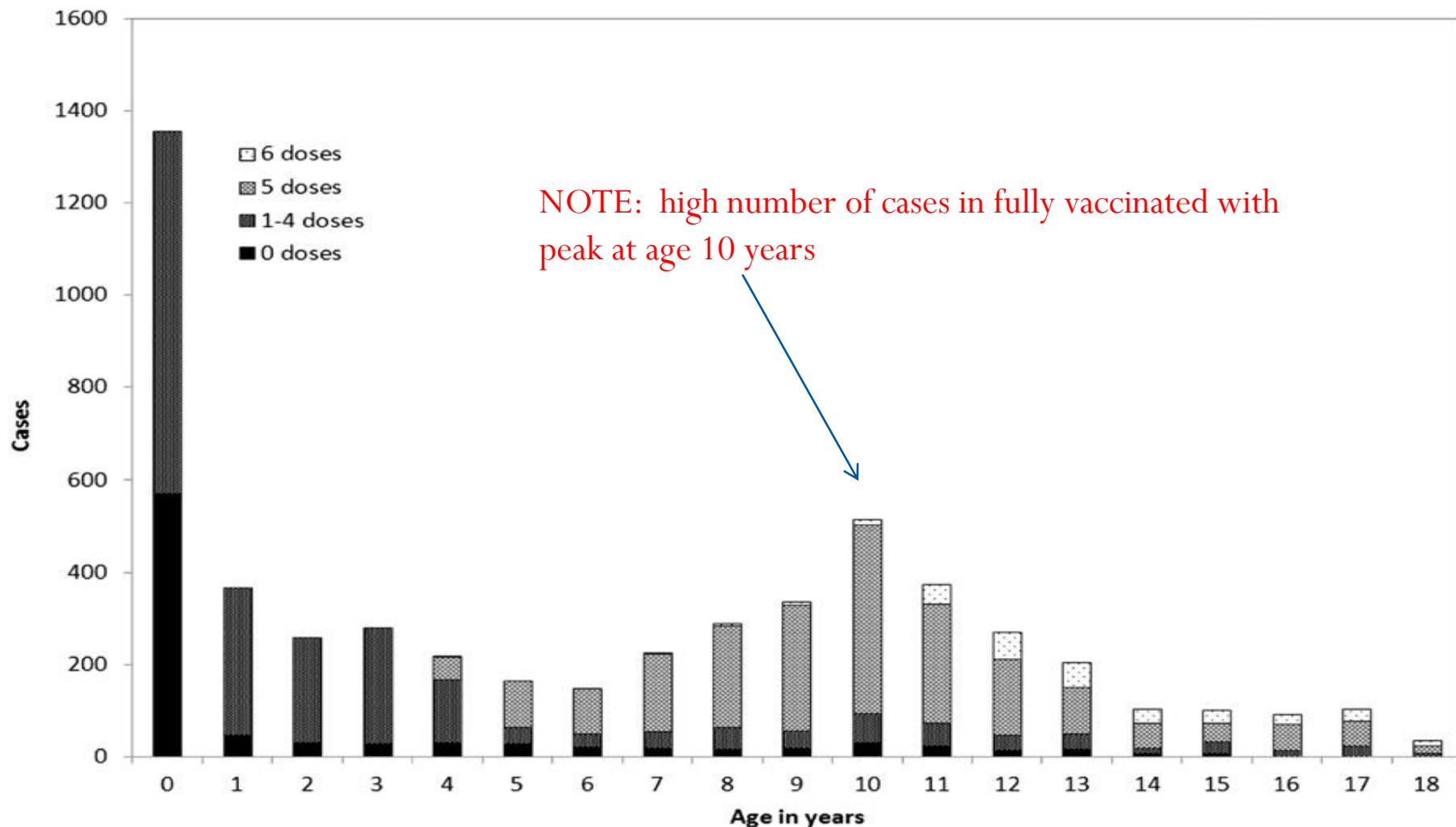
1. <http://www.cdph.ca.gov/HealthInfo/discond/Documents/CherryPertussisInYoungInfants2011-06-20.pdf>

2. JPIDS January 2013

Vaccination data

- Vaccination data available in 76% of those 6m-18 years
- 9% unvaccinated
 - 67% white (31% of child Californians are white)
- 37% incompletely vaccinated
- 55% fully immunized, most in the 7-10 year age range (not yet eligible for Tdap)

Number of pediatric pertussis cases* California, 2010



*of 58% of cases with complete vaccine history data by age and vaccination status: California, 2010.

Public health response: mitigation strategies

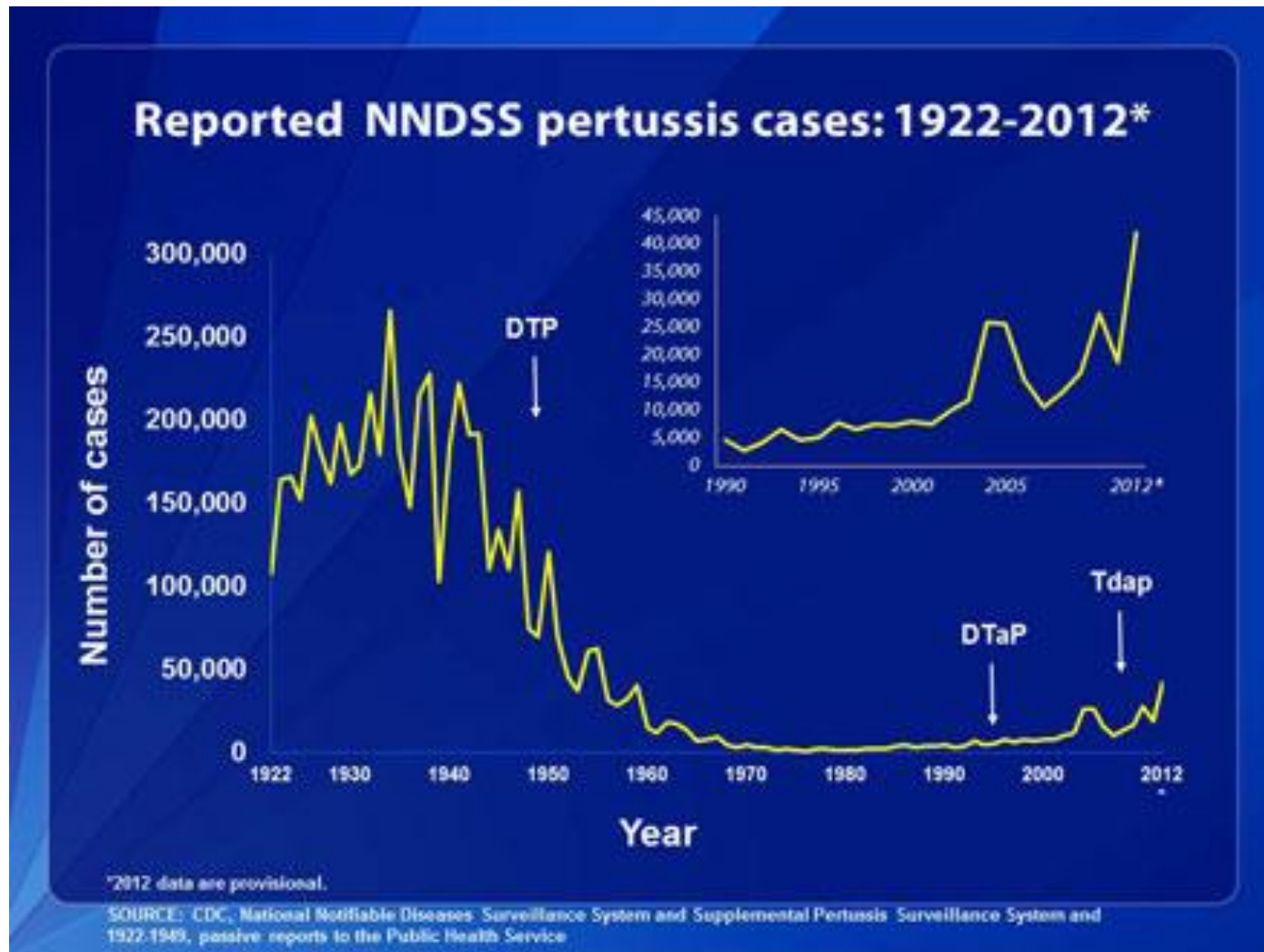
- Clinical guidance on diagnosis and treatment
- Vaccine recommendations including those >64 years, underimmunized 7-9 years, and pregnant women with no minimum interval since last tetanus containing vaccine
- CDPH purchased Tdap and gave at no cost to hospitals, community centers and tribal clinics for pregnant, post partum and other child contacts

What was c/w prior outbreaks

- Rates in young infants
- High rates in Hispanic infants
 - Young age r/o genetic cause and may relate to larger households/susceptibles
- Tdap protected adolescents
- Missing: no data on chemoprophylaxis*

*Contact tracing requires on average 20+ phone calls/exposure, at peak 50 cases/d reported
Cost of contact tracing based on NE outbreak MMWR 2008 26 cases--\$52,000 (\$2000/case)

Pertussis – 41,000 cases in 2012



Unexpectedly Limited Durability of Immunity Following Acellular Pertussis Vaccination in Preadolescents in a North American Outbreak

Witt MA, Katy PH, Witt DJ. Clin Infect Dis 2012;54:1730

Background: Pertussis is prevalent despite widespread acellular pertussis vaccination

Methods: CA outbreak 2010; Marin Cty KP rec PCR testing
Assessed immunization records of cases

Results: 132 PCR+ pediatric cases
Rate PCR+ low 0-6 years
Rate PCR+ high 8-12 years
Vaccine effectiveness 41% 2-7 years
24% 8-12 years
79% 13-18 years

Conclusion: Acellular vaccine/schedule less effective than thought previously

Pertussis Vaccine Effectiveness and the California 2010 Pertussis Outbreak

Roger Baxter, Joan Bartlett, Bruce Fireman, Ali Rowhani-Rahbar, Nicola Klein

1. **DTaP (5th dose) waning** (Presented elsewhere¹)

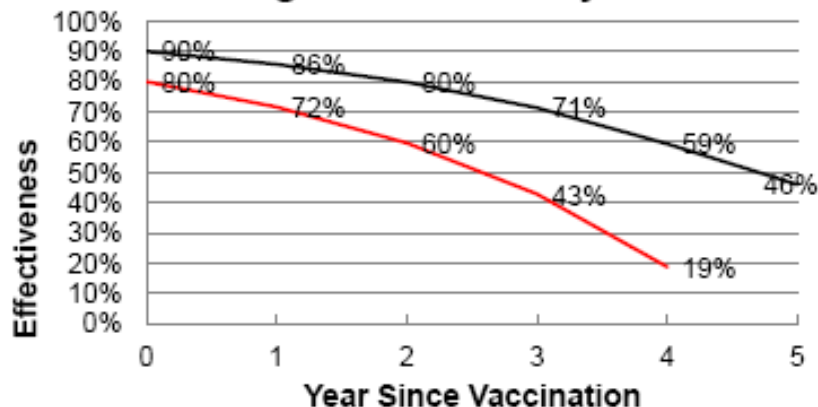
Table: Probability of a positive PCR pertussis test, based on each year after the vaccine

Control Type	Cases N	Controls N	Odds Ratio	95% CI	P-value
PCR Negative	277	3,308	1.415	(1.209, 1.657)	< 0.001
KPNC Pop	277	6,086	1.504	(1.132, 1.998)	0.005

➤ Interpretation: DTaP wanes by 42% per year, each year after administration.

- The graph shows how, for a vaccine with initial effectiveness of 80 or 90%, the effect will wane over 5 years.

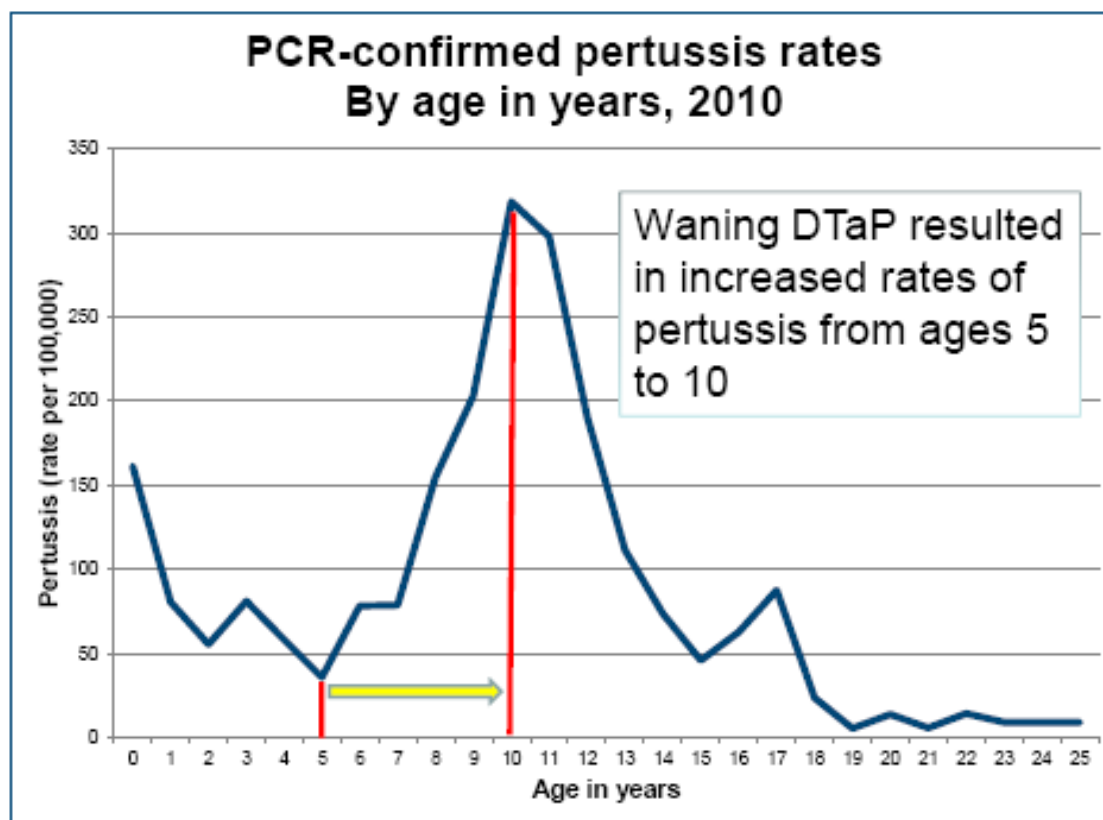
Waning of DTaP each year



Pertussis Vaccine Effectiveness and the California 2010 Pertussis Outbreak

Roger Baxter, Joan Bartlett, Bruce Fireman, Ali Rowhani-Rahbar, Nicola Klein

1. Increasing rates in 5-10 year old children correspond to waning of effect after the 5th dose of DTaP.



EPIDEMIOLOGY AND CONTROL OF PERTUSSIS

- Tdap program has reduced the burden of pertussis in adolescence
- No evidence of Tdap herd protection
- Excellent initial 5-dose DTaP VE (thought 98%)
- Modest but immediate waning immunity post DTaP (95% \rightarrow \leq 83% @ 1 \rightarrow 5 yrs)
- Pertussis burden in children <11 years appears to be a “cohort effect” from change to all aP vaccines (Clark ACIP 2/12)
- aP vaccines are less effective than thought (Witt CID 2012); protection wanes in the 5 years after the 5th dose (Klein NEJM 2012)

Tdap Recommendations and Updates: 2006-2012

Tdap **rec all**
11-12 year olds
Catch-up to 18
Tdap **rec** **adol**
pregnant, AAP

Remove min
interval Tdap/Td
Tdap 7-10 year
olds behind on
DTaP

Tdap **rec all**
HCP
Permissive **rec**
all ≥ 65 years

Tdap **rec all**
pregnant
women at
>20wks, CDC

2006

2011

2012

Cocoon
Tdap **rec**
post-partum,
CDC

Tdap **rec**
<65 year old
contacts

Tdap **rec**
 ≥ 65 year old
contacts

Licensure
Boostrix for
 ≥ 65 -year olds

Tdap **rec all**
 ≥ 11 years
thru any age

Newest Recommendation

- Tdap with every pregnancy during second/third trimester

Question 4

You have made a clinical diagnosis of pertussis in a partially immunized 5 month old with 2 weeks of URI sx's and 5 days of paroxysmal cough. His mother has had a cough for a month. There are 2 other siblings in the home who are behind on immunizations but who have no symptoms. In addition to initiating azithromycin in the infant, what is the next step?

- A. Treat the household
- B. Test the siblings
- C. Immunize the mother
- D. Immunize the siblings
- E. Report the case to DOH

What fuels outbreaks

- Highly contagious
- Large birth cohorts/susceptibles
- Larger unimmunized population/pockets
- Less effective acellular products compared to WC
- Increased detection with awareness and PCR
- Ineffective use of chemoprophylaxis of contacts
- Waning immunity
- Vaccine factors? Inadvertent freezing of vaccine associated with increase in disease in Texas
- Change in organism? Recent sequencing ?mutation

Family Members

75% of sources for infant pertussis

264 cases w known/suspected source identified



20%
Sibling



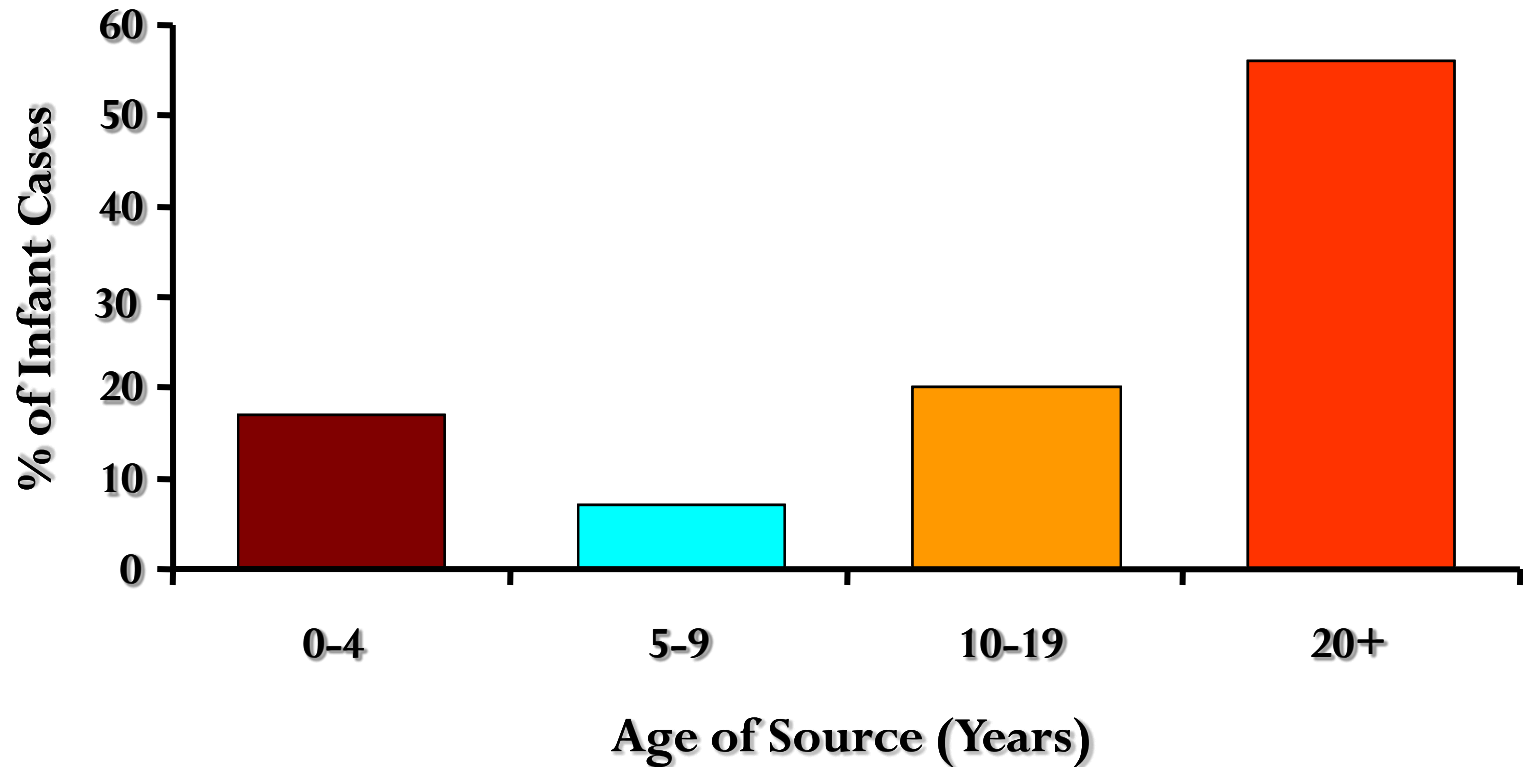
8%
Grandparent



32%
Mom

Bisgard KM, et al. *Pediatr Infect Dis J.* 2004;23:985-989.

Age of Pertussis Source* for Infants



*219 source-persons with known age

Bisgard, K. *PIDJ*. 2004;23:985-9.

Azithromycin and FDA WARNING

- On March 12, 2013, the FDA sent out a Drug Safety Alert advising practitioners that the drug safety labels FOR AZITHROMYCIN had been updated with a stronger warning re: potential for fatal arrhythmias.
- They note that HCP should consider the risk of fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk for cardiovascular events
- The risk of QT prolongation with azithromycin be placed in appropriate context when choosing an antibiotic

HIGH RISK GROUPS

- Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Question 5

A 10 year old with long QT syndrome presents with paroxysmal cough for 2 weeks and you suspect pertussis. Which of the following is an appropriate treatment?

- A. Give no drug and await the disease to run its course
- B. Give amoxicillin
- C. Give TMP/SMX
- D. Give clarithromycin
- E. Call Cindy Olson-Burgess

PROBLEM

- This new warning has pediatricians concerned about the recommendation to provide chemoprophylaxis for household contacts of children with pertussis.
- There are also implications for recommending treatment for those with pertussis and prolonged QTsyndrome.

BACKGROUND

- A May 2012 study published in NEJM by Ray et al identified a small increase in the risk of cardiovascular death in adults (ages 30-74 years) treated with a five-day course of azithromycin .
- The authors noted that the risk of death was higher among patients with a higher baseline risk of cardiovascular disease, and the risk persisted only during the five days of treatment. The risk converts to 47 excess deaths per 1 million prescriptions and increases to 245 per 1 million prescriptions for those with the highest cardiovascular risk profile.
- In August 2012, MAJ and William McConnell alerted AAP members (AAP News) and made recommendations for practitioners, pointing out that most household contacts of children with pertussis are otherwise healthy adults and due diligence should include basic data collection before prescribing any drug (eg, underlying disease, allergies, pregnancy).

ASSESSMENT

- Additional education is needed
- The SADS Foundation publishes lists of drugs to avoid and also divides drugs into 3 categories
 - 1. Drug causes prolonged QT AND substantial risk for TdP (?includes azithromycin after warning; also includes pentamidine, chloroquine, erythromycin, moxifloxacin)
 - 2. Drug causes prolonged QT but insufficient risk for TdP when used as prescribed (includes levofloxacin)
 - 3. Drug causes prolonged QT but risk for TdP only under certain conditions ie excessive dose, drug interaction. (includes TMP-SMX, ciprofloxacin).

RECOMMENDATIONS

- Provide additional education that will
 - Emphasize pediatricians role in pertussis control including chemoprophylaxis (and immunization).
 - Identify screening questions before azithromycin is prescribed for treatment or household prophylaxis
 - Identify drug of choice for pertussis disease or exposure in those with prolonged QT: TMP/SMX or ciprofloxacin (recognizing risks/benefits of each drug)

Hot Off the Press

- Queenan A et al "Peractin-negative variants of Bordetella pertussis in the United States" *N Engl J Med.* 2013; 368: 583-584.
- Liko J et al. "Priming with whole-cell versus acellular pertussis vaccine." *N Engl J Med.* 2013; 368:581-582.

Table 1. Pertussis among Children in Oregon, According to Type of First Dose of Pertussis Vaccine.*

	First Pertussis Vaccine†		Pertussis Cases‡		Incidence per 100,000		Risk Ratio (95% CI)§
	Acellular	Whole Cell	Acellular	Whole Cell	Acellular	Whole Cell	
Any pertussis vaccination¶	164,885	31,074	315	31	191.0	99.8	1.91 (1.32–2.77)
3 pertussis vaccinations in first yr of life	120,712	24,569	243	23	201.3	93.6	2.15 (1.40–3.30)
≥5 pertussis vaccinations starting before 1 yr of age	111,965	22,093	190	18	169.7	81.5	2.08 (1.28–3.38)
≥5 pertussis vaccinations starting before 1 yr of age, and disease at age ≥10 yr	113,502	22,229	130	10	114.5	45.0	2.55 (1.34–4.84)
≥5 pertussis vaccinations starting before 1 yr of age, with Tdap at age ≥10 yr	86,105	16,800	65	5	75.5	29.8	2.54 (1.02–6.36)
Any receipt of Tdap	106,893	17,889	85	6	79.5	33.5	2.37 (1.04–5.42)

* The data apply to children born from 1997 through 1999. Pertussis cases were reported from April 1997 through July 2012. The immunization data for this cohort were reported from March 1997 through July 2012. CI denotes confidence interval, and Tdap the tetanus–diphtheria–acellular pertussis booster.

† Data were stratified according to whether the first pertussis vaccination administered was a whole-cell vaccine (diphtheria–tetanus–whole-cell pertussis, or DTwP) or an acellular vaccine (diphtheria–tetanus–acellular pertussis, or DTaP).

‡ Data were stratified according to whether the first pertussis vaccine was a DTwP or DTaP vaccine, with the first vaccination occurring at least 14 days before disease onset.

§ The risk ratio was calculated as the ratio of the incidence of disease among those first vaccinated with DTaP to the incidence among those first vaccinated with DTwP.

¶ Any pertussis vaccine was defined as at least one reported pertussis-containing vaccination received at least 14 days before disease onset.

Overarching Goals/Recommendations

- Improve Tdap coverage
 - All adults
 - Pregnant women: every pregnancy
 - Catch-up in 7-10 year olds
- Sustain DTaP coverage
 - Unimmunizers
- Lifespan vaccination/boostering
 - ?Potential for herd immunity
- Modify current vaccines
- Novel vaccines

